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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,905	10/01/2001	Shiken Sha	0230-0169P	5513

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EXAMINER	
KEMMERER, ELIZABETH	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 06/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/937,905	SHA ET AL.	
	Examiner	Art Unit	
	Elizabeth C. Kemmerer, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,6,9,11,12,18-21,24,29,31 and 33-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 5, 6, 9, 11, 12, 18-21, 24, 29, 31, and 33-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 19 April 2006 has been entered.

Claims 3, 4, 7, 8, 10, 13-17, 22, 23, 25-28, 30, and 32 are canceled. Claims 1, 2, 5, 6, 9, 11, 12, 18-21, 24, 29, 31, and 33-35 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

The rejection of claims 18-21 and 24 under 35 U.S.C. § 112, second paragraph, as set forth at pp. 3-4 of the previous Office Action (final rejection mailed 23 March 2005) is *withdrawn* in view of the amended and canceled claims.

The rejection of claims 1, 2, 5, 6, 9, 11, 12, 18-21, 24, and 29-33 under 35 U.S.C. § 101 as set forth at pp. 4-6 of the previous Office Action (final rejection mailed 23 March 2005) is *withdrawn* in view of the amended and canceled claims.

The rejection of claims 1, 2, 5, 6, 9, 11, 12, 18-21, 24, and 29-33 under 35 U.S.C. § 112, first paragraph, as set forth at pp. 4-6 of the previous Office Action (final rejection mailed 23 March 2005) is *withdrawn* in view of the amended and canceled claims.

35 U.S.C. § 112, First Paragraph

Claims 1, 2, 5, 6, 9, 11, 12, 18-20, 29, 31, and 33-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated protein comprising the extracellular domain or full-length sequence of SEQ ID NO: 2, as well as isolated nucleic acids encoding the same, vectors comprising the nucleic acid, and isolated transformed host cells comprising the nucleic acid, does not reasonably provide enablement for the claimed invention corresponding to other fragments and variants of SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The instant specification discloses the sequence of the protein of SEQ ID NO: 2, and also discloses the location of the extracellular domain. An isolated nucleic acid sequence encoding the protein (SEQ ID NO: 1) is also disclosed. The specification shows that SEQ ID NO: 2 specifically binds a monoclonal antibody (produced by cell line FERM BP-6103) that induces G-CSF expression. Post-filing date evidence (US Appln. 2004/0052789) has been brought forth that shows that other antibodies binding the extracellular domain of SEQ ID NO: 2 also induce G-CSF production. See US 2004/0052789, Example 7, wherein antibodies APA1 and APA2 induced G-CSF

production whereas antibody APA3 did not. APA1 and APA2 bound the extracellular domain of SEQ ID NO: 2 whereas APA3 bound the intracellular domain. These experiments show that proteins comprising the extracellular domain or the full length of SEQ ID NO: 2 have utility and are enabled for generating and/or purifying antibodies that can induce G-CSF.

However, the claims recite variants of SEQ ID NO: 2 that are not enabled. Specifically, the claims recite proteins having at least 90% identity with the amino acid sequence of SEQ ID NO: 2 through conservative substitution of one or more amino acids wherein the proteins bind to an antibody or an antibody fragment that is active to induce G-CSF. The claims also recite nucleic acids that hybridize to SEQ ID NO: 1 under defined condition and encode a protein that binds the antibodies mentioned above. These encoded protein are not limited to conservative substitutions and thus encompass non-conservative substitutions, insertions, and deletions. However, the specification does not disclose any substitution variants of SEQ ID NO: 2 that can be used to generate active antibodies. The art shows that substitution destroys epitopes in unpredictable ways. For example, McGuiness et al. (1991, The Lancet 337:514-7) report that a point mutation in the *por A* gene causes complete loss of antibody specificity. Daniel et al. (1994, Virology 202 :540-9) disclose that even sophisticated algorithms fail to accurately predict sequences which will act as epitopes.

Generally, the art acknowledges that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many

amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions are generally intolerant of substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

Therefore, in the absence of any specific guidance or working examples, the instant disclosure fails to enable the claimed variants. Due to the large quantity of experimentation necessary to determine which substitution variants of SEQ ID NO: 2 can generate an antibody with the desired activity, the lack of direction/guidance presented in the specification regarding such variants, the absence of working examples directed to any such variants, the complex nature of the invention, the contradictory state of the prior art (see McGuiness et al. and Daniel et al.), the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite limitations regarding which amino acids can be altered, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Applicant argues (p. 7, remarks submitted 19 April 2006) that the examiner has failed to supply supporting evidence or arguments as to why the claimed genus is not enabled. This has been fully considered but is not found to be persuasive for the reasons discussed above, with accompanying evidence and arguments.

Claims 21 and 24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 21 is directed to a screening method for substances. The screening method would only work if the protein of SEQ ID NO: 2 is actually a receptor which, when activated, induces G-CSF production. The specification implies that the protein of SEQ ID NO: 2 behaves in such a manner. However, there is no evidence of such. The specification shows that the monoclonal antibody produced by cell line FERM BP-6103 binds the protein of SEQ ID NO: 2 and induces G-CSF expression. Post-filing date evidence (US Appln. 2004/0052789) has been brought forth that shows that other antibodies binding the extracellular domain of SEQ ID NO: 2 also induce G-CSF production. However, there is no evidence that these antibodies achieve their effect by activating the protein of SEQ ID NO: 2. They could just as readily achieve their effect by antagonizing the protein of SEQ ID NO: 2, which would mean that the protein of SEQ ID NO: 2 is actually an inhibitor of G-CSF induction. If this is the case, then the screening method of claim 21 would not work. In the absence of clarifying evidence, the screening method is not enabled. The following screening methods are suggested for Applicant's consideration: 1) A method of screening for a substance that specifically binds the antibody produced by cell line FERM BP-6103 comprising providing a candidate substance, exposing the candidate substance to said antibody, and testing for specific binding. (Such substances would be useful at least as a label for the antibody.) 2) A method of screening for a substance that specifically binds the protein of SEQ ID NO: 2 comprising providing a candidate substance, exposing the candidate substance to said protein, and testing for specific binding. (Such substances would be useful at least as a label for the protein.)

Claim 24 is directed to a pharmaceutical composition comprising a gene according to claim 1, a protein according to claim 9, or a receptor according to claim 20. The preamble "*pharmaceutical* composition" indicates that the sole intended use for the composition is in therapy. However, the function of the protein (and, by extension, the gene and the receptor) is not known, as discussed above. Therefore, the skilled artisan would not know how to use the claimed pharmaceutical composition. What patients/conditions should be treated? Amending the claim to remove the word "pharmaceutical" would obviate this issue.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 5, 6, 9, 11, 12, 18-21, 24, 29, 31, and 33-35 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 and 18-23 of U.S. Patent Application No. 10/381,710. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons. The instant claims and copending claims are essentially drawn to the same invention, i.e., an isolated gene, its encoded protein, vectors and host cells comprising the gene, and a screening method. The claims differ in the number of variants of SEQ ID NOS: 1 and 2 that are encompassed by the claims. The copending claims encompass a broader genus than the instant claims. However, since the reference sequences are identical (i.e., SEQ ID NOS: 1 and 2), it would have been *prima facie* obvious to the skilled artisan to define increasingly narrow subgenera around SEQ ID NOS: 1 and 2 from the broad genera recited in the copending claims to arrive at the instant claims.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D. can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Elizabeth C. Kemmerer

ECK

ELIZABETH KEMMERER
PRIMARY EXAMINER